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RESEARCH ARTICLE

Evolution of neurologic symptoms in non-hospitalized COVID-19 "long haulers"

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Abstract

Objective: We characterized the evolution of neurologic symptoms and self-perceived recovery of non-hospitalized COVID-19 "long haulers" 6–9 months after their initial Neuro-COVID-19 clinic evaluation. **Methods**: In this follow-up study on the first 100 patients, 50 SARS-CoV-2 laboratory-positive (SARS-CoV-2^{+}), and 50 laboratory-negative (SARS-CoV-2^{-}), evaluated at our Neuro-COVID-19 clinic between May and November 2020, patients completed phone questionnaires on their neurologic symptoms, subjective impression of recovery and quality of life. **Results**: Of 52 patients who completed the study (27 SARS-CoV-2^{+}, 25 SARS-CoV-2^{-}) a median 14.8 (range 11–18) months after symptom onset, mean age was 42.8 years, 73% were female, and 77% were vaccinated for SARS-CoV-2. Overall, there was no significant change in the frequency of most neurologic symptoms between first and follow-up evaluations, including "brain fog" (81 vs. 71%), numbness/tingling (69 vs. 65%), headache (67 vs. 54%), dizziness (50 vs. 54%), blurred vision (34 vs. 44%), tinnitus (33 vs. 42%), and fatigue (87 vs. 81%). However, dysgeusia and anosmia decreased overall (63 vs. 27%, 58 vs. 21%, both $p < 0.001$). Conversely, heart rate and blood pressure variation (35 vs. 56%, $p = 0.01$) and gastrointestinal symptoms (27 vs. 48%, $p = 0.04$) increased at follow-up. Patients reported improvements in their recovery, cognitive function, and fatigue, but quality of life measures remained lower than the US normative population ($p < 0.001$). SARS-CoV-2 vaccination did not have a positive or detrimental impact on cognitive function or fatigue. **Interpretation**: Non-hospitalized COVID-19 "long haulers" continue to experience neurologic symptoms, fatigue, and compromised quality of life 14.8 months after initial infection.

Introduction

As of 20 April 2022, over 506 million people in the world have developed confirmed infection with severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) and over 6.2 million have died from coronavirus disease-2019 (COVID-19).[1] Although much progress has been achieved in the prevention, diagnosis, and treatment of COVID-19 and multiple vaccines have become available, the lasting effects of COVID-19 after the acute phase of the disease have yet to be fully characterized.

Indeed, many infected individuals present with persistent neurologic, pulmonary, cardiac, and gastrointestinal dysfunction following resolution of acute respiratory infection, which has been called the "long-COVID syndrome" or "post-acute sequelae of SARS-CoV-2 infection (PASC).[2–4] Neurologic manifestations of PASC (Neuro-PASC) often occur in people who had mild initial respiratory symptoms and never required hospitalization for pneumonia or hypoxemia, known as COVID-19 "long haulers."[5] While most studies have focused on long-COVID syndrome in previously hospitalized patients, most COVID-19 patients have a mild initial presentation. However, there have been few investigations into long-term effects of COVID-19 in non-hospitalized "long haulers."[6–8] Additionally, while SARS-CoV-2 vaccination

can reduce rates of COVID-19 and death, its effect on long-COVID syndrome remains unclear.[9,10]

In a previous study, we assessed the range of neurologic manifestations in the first 100 non-hospitalized "long haulers" evaluated at our Neuro-COVID-19 clinic over a 9-month period.[11] In this study, we followed up with these patients 6–9 months after their initial visit to characterize the evolution of their neurologic symptoms and self-perceived recovery over time. Moreover, cognitive dysfunction, identified as "brain fog" by "long haulers", has been prominently mentioned in the media and literature.[2,5] Therefore, we tracked the evolution of multiple domains of cognitive function and self-reported quality of life measures using a validated instrument for patient-reported outcomes. Finally, we also sought to characterize patient-perceived recovery and the evolution of cognition and fatigue in both vaccinated and unvaccinated individuals.[9,10]

Subjects/Materials and Methods

Patients inclusion criteria

The current study includes follow-up data from 52 patients who were part of a larger group of 100 patients (the first 50 consecutive SARS-CoV-2 laboratory-positive [SARS-CoV-2^+] and the first 50 consecutive SARS-CoV-2 laboratory-negative [SARS-CoV-2^-] individuals who met inclusion criteria) seen at the Neuro-COVID-19 clinic of Northwestern Memorial Hospital, Chicago, IL between May 13 and November 11, 2020.[11] Those 100 were included in the initial study if they had clinical manifestations of COVID-19 compatible with Infectious Diseases Society of America (IDSA) guidelines[12] starting February 2020 but were not hospitalized for pneumonia or hypoxemia and had neurologic symptoms persisting for at least 6 weeks from symptom onset. COVID-19 diagnosis was confirmed by SARS-CoV-2 reverse transcription-polymerase chain reaction (RT-PCR) of nasopharyngeal swab and/or SARS-CoV-2 antibody testing in 50 SARS-CoV$^-2^+$ patients, whereas either of those tests showed negative results in 50 SARS-CoV-2^- patients.

The current study was a follow-up study on this group of 100 patients. Patients were included if they provided verbal consent and fully completed follow-up questionnaires via email or phone. This study was approved by our institutional review board (STU00212583).

Procedures

This study involved a phone/email follow-up 6–9 months after their first clinic visit. The study staff first contacted each patient via telephone to obtain verbal consent. Once patients provided verbal consent, they were asked about their preference for completing questions either over the phone or entirely over email. For those who preferred survey completion via phone, the Neuro-COVID-19 questionnaire was completed on the concurrent call, and the Patient-Reported Outcome Measurement Information System (PROMIS) questionnaire was sent via email for self-completion. For those who preferred email, both questionnaires were sent via email for self-completion. If patients did not answer the first phone call, phone contact was attempted two more times over the following week before a final email was sent asking about patient interest in participating. If there was no response to the email, the patient was not included in the study.

The Neuro-COVID-19 questionnaire assessed patients' self-perceived recovery, current neurologic, and extra-neurologic symptoms associated with COVID-19, medications tried for COVID-19, and details about COVID-19 vaccination status. The PROMIS questions assessed patient-reported quality of life in cognition and fatigue domains using the Cognitive Function v2.0 Computer-Adaptive Test (CAT) and Fatigue v1.0 CAT. At follow-up, PROMIS v1.0 CAT questions for anxiety, depression, and sleep disturbance were added to our evaluation. PROMIS results are expressed as T-scores with a score of 50 representing the normative mean/median of the US reference population with a standard deviation of 10. Lower cognition T-scores indicate worse performance while higher fatigue T-scores indicate greater fatigue severity.[2,13,14]

Statistical analysis

Statistical analysis was primarily performed using R version 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria) with two-sided $p \leq 0.05$ considered statistically significant. Data were summarized as number of patients (frequency), mean (standard deviation) for normally distributed variables, and median (interquartile range [IQR]) for non-normally distributed variables. Group differences were assessed using Fisher's exact test and unpaired Wilcoxon rank-sum test. Differences between initial clinic visit and follow-up questionnaire time points within groups were assessed using the paired Wilcoxon rank-sum test. Changes in the proportions of reported symptoms across paired initial visit and follow-up time points were assessed using McNemar's exact test. The results of PROMIS T-scores at follow-up were compared to the normative US population median of 50 using one-sample Wilcoxon signed-rank tests. Study data were collected and managed using REDCap electronic data capture tools. Results of PROMIS measures for cognition, fatigue, anxiety, depression, and sleep collected at

the second visit were analyzed by Spearman correlation with r values depicted in a heatmap matrix, and the relationship between cognition and other PROMIS domains were compared by simple linear regression, both performed using GraphPad Prism v9.0.0 (GraphPad Software, La Jolla, CA, USA).

Results

Patient demographics, response rate, and vaccination status

Of the 100 patients seen in the Neuro-COVID-19 clinic included in our initial study, 66% of patients consented to be included in the follow-up study, and 5% of patients declined, for a total response rate of 71% without significant difference between the SARS-CoV-2 laboratory positive (SARS-CoV-2^+) and laboratory-negative (SARS-CoV-2^-) groups. Of the 66 consented patients, 52 completed the follow-up study a median 14.8 months after symptom onset (range 11–18 months), of whom 27 were SARS-CoV-2^+ and 25 were SARS-CoV-2^-.

Among these 52 patients, the mean age was 42.8 ± 11.5 years, median BMI was 25.4 (IQR 22.2, 29.9), 73% were female, and 90.3% were white. Of all patients, 77% had been vaccinated between the first clinic visit and follow-up. There were no significant differences between the SARS-CoV-2^+ and SARS-CoV-2^- groups for any of these demographic variables. However, SARS-CoV-2^+ patients reported receiving their most recent COVID-19 vaccine (considered as either the second doses of Pfizer and Moderna or the first dose of Johnson & Johnson) at a longer period prior to follow-up than did SARS-CoV-2^- patients (a median of 110 days before follow-up vs. 57 days, respectively). Patient demographics and vaccination background are outlined in Table 1.

Frequency of neurologic symptoms and signs attributed to COVID-19

Overall, patients reported a median of five neurologic symptoms on follow-up, which was similar to the initial evaluation. However, there was an overall decrease in the frequency of patients experiencing four or more neurologic symptoms, going from 81% to 62% ($p = 0.02$), which was principally driven by the SARS-CoV-2^+ group (78% vs. 48%, $p = 0.04$), whereas a nonsignificant decrease was observed in the SARS-CoV-2^- group (84% vs. 76%, $p = 0.63$). Compared to the initial visit, there was no significant difference in the frequency of SARS-CoV-2^+ and SARS-CoV-2^- patients endorsing neurological symptoms of brain fog, headache, numbness/tingling,

Table 1. Study respondents' demographics, response rate, and vaccination status by SARS-CoV-2 result.

	Overall	SARS-CoV-2^+	SARS-CoV-2^-	*p*
n	52/100	27/50	25/50	0.84
Follow-up period, months (median [IQR])	9.2 [9.0, 9.6]	9.4 [9.1, 10.0]	9.2 [8.8, 9.4]	0.06
Time from onset, months (median [IQR])	14.8 [13.5, 16.0]	14.3 [12.8, 16.0]	14.9 [13.6,16.1]	0.73
Age, years (mean (1 SD))	42.8 (11.5)	45.3 (12.5)	40.0 (9.9)	0.13
Male, *n* (%)	14 (27)	9 (33)	5 (20)	0.36
Female, *n* (%)	38 (73)	18 (66)	20 (80)	
BMI (median [IQR])	25.4 [22.2, 29.9]	25.8 [23.7, 29.9]	23.5 [20.8, 30.3]	0.28
BMI > 25, *n* (%)	27 (52)	17 (63)	10 (40)	0.16
BMI > 30, *n* (%)	12 (23)	5 (19)	7 (28)	0.52
Race, *n* (%)				
White	47 (90)	23 (85)	24 (96)	0.24
Black	1 (2)	0 (0)	1 (4)	
Asian	2 (4)	2 (7)	0 (0)	
American Indian or Alaskan Native	0 (0)	0 (0)	0 (0)	
Other	2 (4)	2 (7)	0 (0)	
Vaccination status, *n* (%)				
Vaccinated	40 (77)	22 (81)	18 (72)	0.49
Pfizer	28 (70)	14 (64)	14 (78)	0.73
Moderna	10 (25)	7 (32)	3 (17)	
J&J	2 (5)	1 (5)	1 (6)	
Days between last[a] vaccination and follow-up (median [IQR])	94 [42.2, 128]	110 [68.2, 130]	57 [14.2, 106]	**<0.05**

p values <0.05 are marked in bold.

[a]Second dose of Moderna and Pfizer or first dose of J&J.

dizziness, pain other than chest, blurred vision, and tinnitus.

The frequency of patients reporting dysgeusia significantly decreased from initial clinic visit to follow-up overall (63% vs. 27%, $p < 0.001$) and in SARS-CoV-2$^+$ patients (70% vs. 26%, $p < 0.01$); the frequency of dysgeusia in SARS-CoV-2$^-$ patients also trended downwards on follow-up (56% vs. 28%, $p = 0.09$). Similarly, anosmia decreased significantly from initial clinic visit to follow-up overall (58% vs. 21%, $p < 0.0001$), as well as among SARS-CoV-2$^+$ patients (78% to 33%, $p < 0.001$) and SARS-CoV-2$^-$ patients (36% vs. 8%, $p = 0.02$). In addition, there were no significant changes in the frequency of non-neurologic symptoms including fatigue, depression/anxiety, shortness of breath, chest pain, and insomnia, but there was an increase in frequency of reported variation in heart rate and blood pressure (35% vs. 56%, p = 0.01) and gastrointestinal symptoms (27% vs. 48%, $p = 0.04$) in the overall population. The frequencies of neurologic and non-neurologic symptoms are shown in Table 2.

Interestingly, whereas some patients' symptoms had resolved at the time of follow-up, others developed new symptoms. The proportions of subjects reporting changes in each neurologic and non-neurologic symptom between initial clinic visit and follow-up are outlined in the Table S1.

Medications tried

Medications tried for persistent neurological symptoms in the time between first clinic visit and follow-up is shown in Table 3. Of all patients, 54% used new medications for control of their neurologic symptoms. Among the medications taken, the most frequent were those for neuropathic pain (61%), followed by alternative medicine/supplements (36%) and antidepressants (29%).

Assessment of subjective perception of recovery and quality of life

We then compared the evolution of patients' subjective impression of recovery relative to their pre-COVID-19 baseline between the initial clinic visit and follow-up. Changes in subjective impression of recovery were heterogeneous across both SARS-CoV-2$^+$ and SARS-CoV-2$^-$ groups, with some subjects reporting improvement on follow-up relative to the initial clinic visit while others reported that their overall condition had worsened since the initial clinic visit (Fig. 1). Overall, patients did report improvements in their subjective impression of recovery, with a median recovery at follow-up of 75% compared to 65% on initial clinic visit ($p = 0.02$). When evaluated by SARS-CoV-2 status, both groups generally reported

Table 2. Neurologic and other symptoms endorsed by patients, compared between initial clinic visit and follow-up, by SARS-CoV-2 result.

	Overall ($n = 52$)			SARS-CoV-2$^+$ ($n = 27$)			SARS-CoV-2$^-$ ($n = 25$)		
Symptom	First visit	Follow-up	*p*	First visit	Follow-up	*p*	First visit	Follow-up	*p*
Neurologic symptoms attributed to COVID-19 (median [IQR])	5 [4,6]	5 [2,6.25]	0.19	5 [4,5.5]	3 [1.5,6]	0.10	6 [4,7]	6 [4,8]	1
Neurologic symptoms, *n* (%)									
≥4	42 (81)	32 (62)	**0.02**	21 (78)	13 (48)	**0.04**	21 (84)	19 (76)	0.63
Brain fog	42 (81)	37 (71)	0.27	21 (78)	16 (59)	0.13	21 (84)	21 (84)	1
Numbness/tingling	36 (69)	34 (65)	0.79	16 (59)	14 (52)	0.73	20 (80)	20 (80)	1
Headache	35 (67)	28 (54)	0.14	16 (59)	13 (48)	0.51	19 (76)	15 (60)	0.29
Dysgeusia	33 (63)	14 (27)	**<0.001**	19 (70)	7 (26)	**<0.01**	14 (56)	7 (28)	0.09
Anosmia	30 (58)	11 (21)	**<0.0001**	21 (78)	9 (33)	**<0.001**	9 (36)	2 (8)	**0.02**
Dizziness	26 (50)	28 (54)	0.80	10 (37)	11 (41)	1	16 (64)	17 (68)	1
Pain other than chest	21 (40)	23 (44)	0.82	9 (33)	9 (33)	1	12 (48)	14 (56)	0.75
Blurred vision	19 (37)	23 (44)	0.48	4 (15)	8 (30)	0.34	15 (60)	15 (60)	1
Tinnitus	17 (33)	22 (42)	0.18	5 (19)	7 (26)	0.63	12 (48)	15 (60)	0.38
Other symptoms, *n* (%)									
Fatigue	45 (87)	42 (81)	0.51	23 (85)	22 (81)	1	22 (88)	20 (80)	0.69
Depression/Anxiety	34 (65)	28 (54)	0.29	18 (67)	15 (56)	0.55	16 (64)	13 (52)	0.55
Insomnia	24 (46)	30 (58)	0.18	12 (44)	14 (52)	0.63	12 (48)	16 (64)	0.34
Shortness of breath	24 (46)	19 (37)	0.38	8 (30)	7 (26)	1	16 (64)	12 (48)	0.39
Chest pain	18 (35)	17 (33)	1	4 (15)	7 (26)	0.45	14 (56)	10 (40)	0.34
Variations in HR & BP	18 (35)	29 (56)	**0.01**	5 (19)	11 (41)	0.07	13 (52)	18 (72)	0.18
GI symptoms	14 (27)	25 (48)	**0.04**	7 (26)	12 (44)	0.23	7 (28)	13 (52)	0.18

p values <0.05 are marked in bold.

Table 3. Treatment types tried for COVID-19 prior to follow-up.

	Overall (n = 52)	SARS-Cov-2$^+$ (n = 27)	SARS-Cov-2$^-$ (n = 25)
Any treatment, n (%)	28/52 (54)	13/27 (48)	15/25 (60)
Neuropathic pain	17 (61)	8 (62)	9 (60)
Alternative/supplement	10 (36)	7 (54)	3 (20)
Antidepressant	8 (29)	3 (23)	5 (33)
Antacid	5 (18)	3 (23)	2 (13)
Benzodiazepine	5 (18)	1 (8)	4 (27)
Migraine preventive	5 (18)	3 (23)	2 (13)
Beta blocker	4 (14)	2 (15)	2 (13)
Migraine abortive	4 (14)	2 (15)	2 (13)
Sleep	4 (14)	2 (15)	2 (13)
Antihistamine	3 (11)	1 (8)	2 (13)
Anti-inflammatory	2 (7)	1 (8)	1 (7)
Narcotic analgesic	1 (4)	1 (8)	0 (0)
Neuromuscular blocker	1 (4)	1 (8)	0 (0)

improvements in impression of recovery, with significant improvement observed in the SARS-CoV$^-$2$^+$ subjects (median 75% on follow-up compared to 70% on initial visit, p = 0.04).

We also compared PROMIS quality of life T-scores between the initial clinic visit and follow-up for cognitive function and fatigue domains. PROMIS T-scores trended toward improved cognitive function (median 34 vs. 38.2; p = 0.13) and decreased fatigue (64 vs. 60.4, p = 0.13) in SARS-CoV-2$^+$ patients. Of note, similar trends were observed in SARS-CoV-2$^-$ patients, with a decreasing trend in fatigue T-scores (median 66.5 vs. 60.8, p = 0.16) and significant improvement in cognitive function from initial visit to follow-up (median 33 vs. 40.3, $p < 0.01$).

The magnitudes of change in PROMIS T-scores for both cognitive function and fatigue domains were not significantly different between SARS-CoV-2$^+$ and SARS-CoV-2$^-$ groups. Nevertheless, even at time of follow-up, patients from both groups continued to report significantly worse PROMIS quality of life for cognition and fatigue T-scores compared to the US median PROMIS T-score of 50 ($p < 0.001$ for both cognition and fatigue). Indeed, despite improvement, T-scores at follow-up remained in ranges indicative of mild cognitive dysfunction and fatigue (Fig. 2).

To characterize further associations between quality of life measures of cognition and other neuropsychiatric domains, we compared PROMIS T-scores for cognitive function with those of fatigue, as well as anxiety, depression and sleep disturbance that were only measured at follow-up. A low cognitive function was significantly correlated with worse fatigue, anxiety, depression, and sleep disturbance (Fig. S1).

Effect of SARS-CoV-2 vaccines on subjective recovery and quality of life

We then explored whether SARS-CoV-2 vaccination affected subjective impression of recovery and quality of life (Table 4). Of 50 individuals who provided this information, 40 had received vaccines (Table 1) and 10 were unvaccinated. In both vaccinated and unvaccinated patients, the subjective impression of recovery increased at follow-up relative to initial clinic visit. The subjective recovery in vaccinated patients trended upwards between the two time points (median 67.5% vs. 75%, p = 0.1) and improved significantly in the unvaccinated patients (median 45% vs. 62.5%, p = 0.03), although the unvaccinated patient group was small relative to the vaccinated group (n = 10 vs. n = 40). The magnitude of this increase in subjective recovery between follow-up and initial visit was also significantly greater in unvaccinated than vaccinated patients (20% increase vs. 5% increase, p = 0.02). Retrospective analyses revealed that patients who would go on to become vaccinated had reported significantly higher impression of recovery at the initial clinic visit (median 67.5% vs. 45%, p = 0.03) and subsequently endorsed higher impression of recovery at follow-up compared to the unvaccinated group (median 75% vs. 62.5%, p = 0.53).

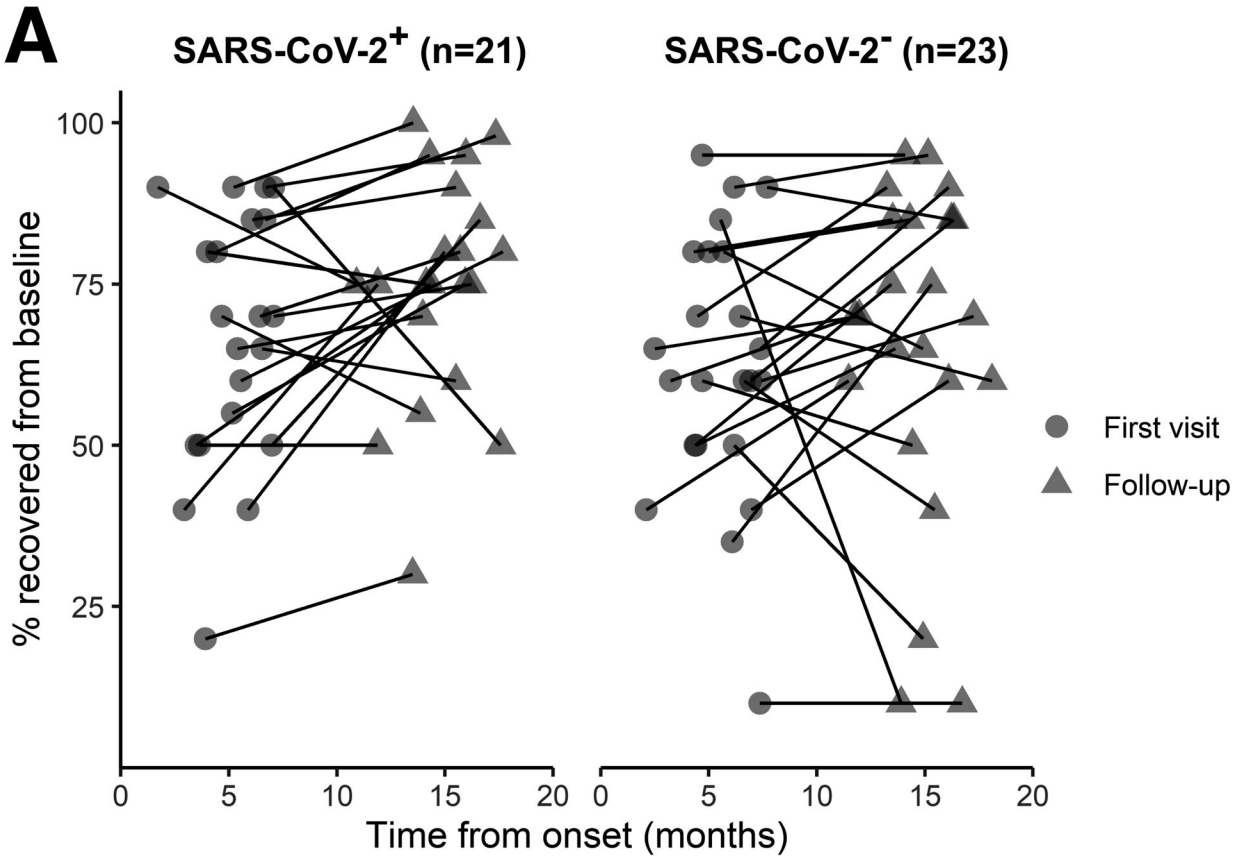
Quality of life PROMIS T-scores for cognition increased significantly in vaccinated individuals only (median 34 vs. 40.8, $p < 0.01$), whereas there was no significant change in either group in PROMIS T-score for fatigue between the initial clinic visit and follow-up. Finally, the magnitude of change in quality-of-life PROMIS T-scores for cognition and fatigue between initial visit and follow-up was also not significantly different for vaccinated and unvaccinated patients.

Discussion

Rationale for inclusion of SARS-CoV-2-negative individuals with post-viral syndrome and definition of long-COVID in non-hospitalized patients

We followed up on the neurologic symptoms and quality of life measures in the first 100 non-hospitalized SARS-CoV-2$^+$ and SARS-CoV-2$^-$ "long haulers" initially evaluated between May and November 2020 at our Neuro-COVID-19 clinic. We included by design patients who tested negative for SARS-CoV-2 either by nasal swab RT-PCR or by serology, who constituted half of our clinic population at the time.

Our decision to include SARS-CoV-2$^-$ patients was deliberate, and motivated by the following facts: (1) The

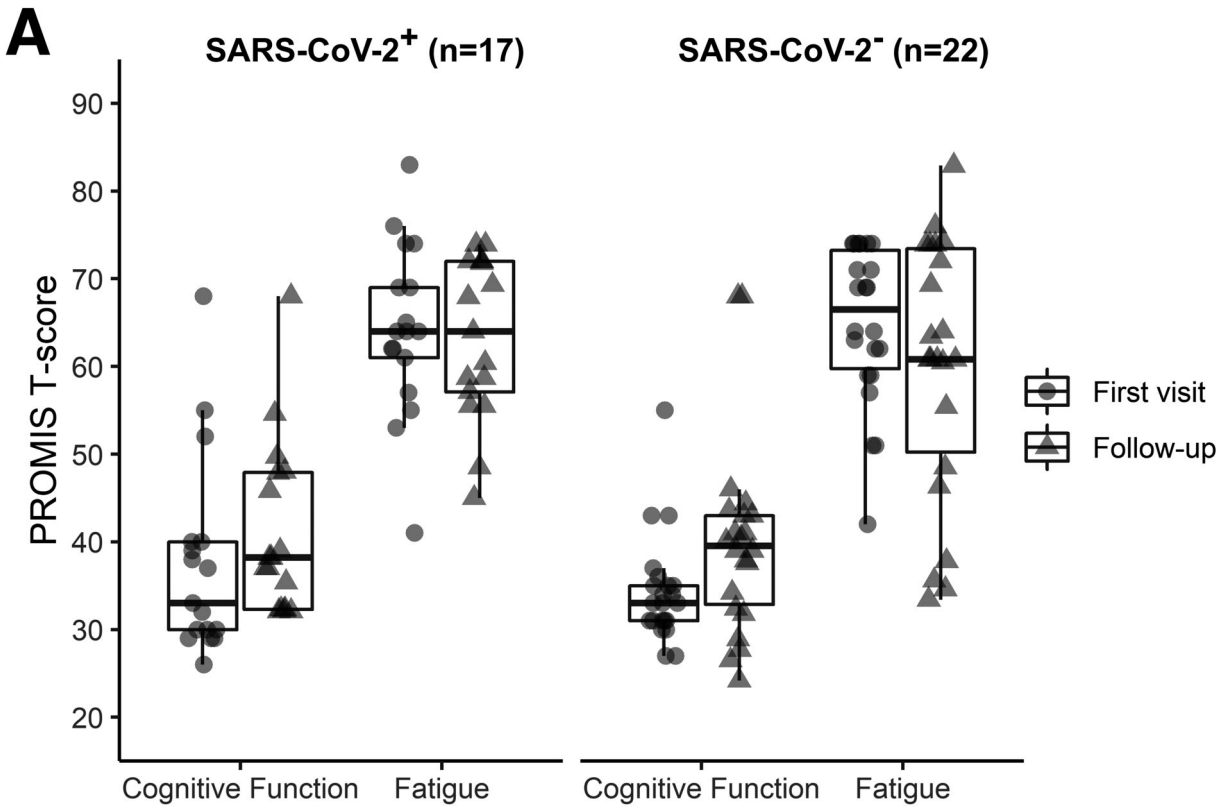


B

	Subjective impression of % recovery (median [IQR])		
	First visit	Follow-up	*p*
Overall	65 [50,80] (n=47)	75 [60,85] (n=49)	**0.02 (n=44)**
SARS-CoV-2+	70 [52.5,85] (n=23)	75 [55,85] (n=25)	**0.04 (n=21)**
SARS-CoV-2-	60 [50,80] (n=24)	70 [60,85] (n=24)	0.25 (n=23)

Figure 1. Subjective impression of percent recovery from pre-COVID-19 baseline at first clinic visit (circles) and follow-up (triangles) relative to time from COVID-19 symptom onset, displayed by SARS-CoV-2 status. Each subject is represented by a pair of connected points, with overlapping time points and percent recoveries illustrated by increased point opacity. Only subjects with paired responses from the initial clinic visit and follow-up survey are represented in the Figure. A pre-COVID-19 baseline of 100% was assumed. *p* values <0.05 are indicated in bold in the table.

difficulty or impossibility for patients with mild respiratory symptoms to be tested by nasopharyngeal swab RT-PCR at the beginning of the pandemic; (2) The false negative RT-PCR rate increasing after day 3 of symptom onset, when the false negative rate is 20%, reaching 66% by day 21 suggesting that 54% patients could have an initial RT-PCR false negative result[15,16]; (3) The low sensitivity of the first commercially available anti-Nucleocapsid serology test (Abbott)[17–19]; (4) Rapidly decaying anti-Nucleocapsid antibody titers[20–27]; (5) Males are likely to retain antibodies longer than females, and antibody tests can be less accurate for females.[28,29] This is relevant to our cohort of whom the majority was female (73%). (6) Among the SARS-CoV-2 $^{+}$ patients in the initial study, only 32% had both RT-PCR and anti-Nucleocapsid ab positive tests, and some had one test positive while the



B

	PROMIS Domain T-score (median [IQR])					
	Cognition			Fatigue		
	First visit	Follow-up	*p*	First visit	Follow-up	*p*
SARS-CoV-2+	34 [30,39.5] (n=19)	38.2 [33.9,48.0] (n=23)	0.13	64 [61.5,71.5] (n=19)	60.4 [56.3,71.9] (n=23)	0.81
SARS-CoV-2-	33 [31,35] (n=19)	40.3 [33.8,43.3] (n=24)	**<0.01**	66.5 [59.8,73.25] (n=22)	60.8 [53.7,72.5] (n=24)	0.16
	SARS-CoV-2+	SARS-CoV-2-	*p*	SARS-CoV-2+	SARS-CoV-2-	*p*
Δ T-score	6.3 [0,11] (n=17)	4.3 [0.87,9.5] (n=22)	0.91	0.5 [-6.1,6.8] (n=17)	-3.7 [-10.5,3.0] (n=22)	0.40

Figure 2. PROMIS Quality of Life domain scores for cognitive function and fatigue, by SARS-CoV-2 result. (A) T-scores from the first clinic visit (circles) and follow-up (triangles) are displayed against respective boxplots (outliers displayed as solid circles), grouped by SARS-CoV-2 status. Only subjects with T-scores from both the initial clinic visit and follow-up are displayed. (B) Differences between first visit and follow-up T-scores were compared by SARS-CoV-2 status with paired analyses, while changes in T-scores across paired timepoints in individual patients were compared between SARS-CoV-2 groups with unpaired analyses. *p* values <0.05 are indicated in bold in the table.

other test was negative, indicating the low sensitivity of those tests,[11] and (7) SARS-CoV-2$^-$ patients were included only if they had infectious disease society of America (IDSA) clinical symptoms of COVID-19.[12] In addition, based on the WHO COVID-19 case definitions released in December 2020 (after enrollment of the first 100 patients in our initial study), 16/25 (64%) SARS-CoV-2$^-$ patients in our current study are considered "probable" cases of SARS-CoV-2 infection due to dysgeusia and/or anosmia in the absence of any other identified cause, while the remaining 9/25 (36%) are "suspected" cases.[30]

Among both post-hospitalized and non-hospitalized patients, the definition of long-COVID syndrome is still unclear. The CDC defines post-COVID conditions as "a wide range of new, returning, or ongoing health problems

Table 4. PROMIS Quality of Life domain scores for cognition and fatigue and subjective impression of percent recovery from pre-COVID baseline, by vaccination status at follow-up.

	Subjective impression of % recovery (median [IQR])			PROMIS Domain T-score (median [IQR])					
				Cognition			Fatigue		
	First visit	Follow-up	*p*	First visit	Follow-up	*p*	First visit	Follow-up	*p*
Vaccinated (n = 40)	67.5 [60,80]	75 [60,85]	0.10	34 [30.8,38.3]	40.8 [36.6,45.9]	<0.001	67 [60.5,74]	60.6 [54.2,71.85]	0.10
Unvaccinated (n = 10)	45 [40,55]	62.5 [60,75]	0.03	32 [30.75,34.25]	35 [32.3,39]	0.62	64 [60.8,71.8]	64 [60.5,73.9]	1
	Vaccinated	Unvaccinated	*p*	Vaccinated	Unvaccinated	*p*	Vaccinated	Unvaccinated	*p*
Δ over time	5 [−5,14]	20 [13.8,27.5]	0.02	5.55 [0.87,10.9]	3.65 [−3.15,6.375]	0.36	−2.65 [−10.1,3]	6.2 [−10.9,9.9]	0.33

p values <0.05 are marked in bold.

people can experience four or more weeks after first being infected with the virus that causes COVID-19. Even people who did not have COVID-19 symptoms in the days or weeks after they were infected can have post-COVID conditions."[31] For this study, we defined long-COVID syndrome as symptoms lasting longer than 6 weeks, based on expectations that the majority of patients recovered from acute viral illness by 4 to 6 weeks.[32–34]

Evolution of neurologic symptoms at follow-up

At a median of 9.2 months after their first visit, there was no significant change in the frequency of most neurological and non-neurological symptoms attributed to COVID-19 overall, suggesting continued significant symptom burden of long-COVID syndrome on patients lasting a median of 14.8 months overall after symptom onset. The persistence of these symptoms led over half of the "long haulers" in our study to trial a variety of treatments, the most frequent being medications for neuropathic pain, alternative/supplements, and antidepressants.

However, we saw a significant overall decrease in the prevalence of anosmia and dysgeusia between the initial clinic and follow-up, suggesting a favorable long-term prognosis for olfactory and gustatory dysfunction in "long haulers." These findings are consistent with those of other studies.[35–37] Conversely, we observed a significant increase in the prevalence of heart rate and blood pressure variation and gastrointestinal symptoms in the overall study population at follow-up. Autonomic dysfunction has been previously noted in "long hauler" patients as a possible cause of such symptoms, and it is hypothesized that dysfunction could be due to ongoing cytokine release or viral-mediated mechanisms.[38] Although the etiology of this dysautonomia is still unclear, the fact that it can present later in the long-COVID syndrome and persist over time can inform management of long-COVID and care for "long hauler" patients.

Evolution of subjective impression of recovery and quality of life scores at follow-up

While individual evolution was heterogeneous, patients overall perceived improvement in their recovery, which was significant in the SARS-CoV-2^{+} group. These results are important given that at follow-up, there was no significant change in frequency of many neurological symptoms, although subjective impression of recovery improved from 65% to 75% overall. This could be caused by a combination of factors, including the use of symptomatic medications, resolution of hallmark symptoms such as anosmia and dysgeusia, or decrease in symptom severity over time.

Overall, patients reported improving cognitive function and decreased fatigue at follow-up, and this improvement was significant for the cognitive domain in SARS-CoV-2^{-} patients, providing hopeful data for improved quality of life in "long haulers" over time. However, the magnitude was not different between SARS-CoV-2 groups, and the median quality of life values remained significantly lower than those of the US normative population a median 14.8 months after symptom onset. Furthermore, quality of life measures also indicated the interconnection of cognitive function with fatigue, anxiety, depression, and sleep disturbance domains.

Comparison of vaccinated and unvaccinated patients' recovery and PROMIS scores

There was favorable evolution in both vaccinated and unvaccinated individuals for subjective impression of

recovery and patient-reported cognition. This improvement was significant for cognition in vaccinated patients and for the subjective percent recovery in unvaccinated patients. Although vaccinated patients trended toward decreased fatigue at follow-up, this was not significant, and unvaccinated patients demonstrated minimal change in PROMIS fatigue scores.

There have been media reports that vaccination cures long-COVID in some patients, but our data do not support these claims.[39–41] However, these results should allay the fear of long-COVID relapse in patients reluctant to get vaccinated. Of note, all available vaccines elicit antibodies to the spike protein of SARS-CoV-2, rendering initially SARS-CoV-2 laboratory-negative "long-haulers" seropositive, thereby making them indistinguishable from those who were initially SARS-CoV-2 antibody-positive due to SARS-CoV-2 infection. To determine if patients initially serologically negative for SARS-CoV-2 nucleocapsid protein have actually been exposed to the virus, we are currently studying their T-cell response to nucleocapsid peptides, which is not affected by vaccination with the spike protein. These studies, outside of the scope of the present manuscript, are currently ongoing in our laboratory.

Comparison with other long-COVID studies

Although we define long-COVID syndrome as symptoms presenting for more than 6 weeks, some studies describe long-COVID as persistent symptoms lasting greater than 4 weeks with fatigue, headache, and anosmia as prevalent symptoms.[6,7,32–34] In addition to these symptoms, our cohort demonstrates that brain fog and depression/anxiety occur at high frequency at follow-up, suggesting their relevance to long-COVID syndrome. In a prospective cohort study in Arizona, 68.7% of nonhospitalized "long haulers" had persistent symptoms 1-month postinfection, with a median of 3 symptoms.[6] In our cohort, 94.2% of patients had at least one persistent symptom at follow-up, and overall, patients still had a median of five different neurologic symptoms 11–18 months after symptom onset. Beyond 12 weeks of follow-up, one study reported that 40% of non-hospitalized "long haulers" in Denmark had symptoms including fatigue (16%) and concentration difficulties (13%).[7] Our study demonstrated a much higher prevalence of fatigue with 81% of SARS-CoV-2$^+$ patients endorsing fatigue at follow-up, which could be explained by the fact that we studied self-selected patients attending a clinic appointment for neurologic symptoms, in contrast to a cohort obtained from the Danish national registry. Beyond 4 months from onset, one study reported that half of nonhospitalized COVID-19 patients experience at least one persisting symptom.[42] Three to 8 months from onset, another study showed that 36% of non-hospitalized COVID-19 patients reported worsened health, while only 18% of SARS-CoV-2$^-$ patients reported a similar deterioration, suggesting a long-term burden of COVID-19 that may last months beyond initial infection.[8] Altogether, our study patients displayed a greater symptom burden at follow-up than other published reports. It is possible that patients who came to our clinic had more severe long-COVID syndrome at baseline relative to the average non-hospitalized "long hauler," which influenced their decision to seek care. Nevertheless, this high symptom burden in "long haulers" suggests that research efforts need to shift from defining prevalence and mortality of COVID-19 to characterizing patient recovery and long-term symptom evolution.

Study limitations and future directions

A primary limitation of our study is the small sample size, which could have reduced the power of analyses to detect significant differences between the SARS-CoV-2$^+$ and SARS-CoV-2$^-$ groups from initial to follow-up visits. However, our 52% retention rate is similar or higher than other follow-up studies, which have mainly been performed in previously hospitalized COVID-19 patients[43–45] and rarely in nonhospitalized individuals,[46] and the demographics, symptomatology, and even breakdown of SARS-CoV-2$^+$ to SARS-CoV-2$^-$ patients in our patient population parallels that of the initial study. Of note, 77% of our patients were fully vaccinated as per CDC guidelines, which is higher than the 51.6% vaccination rate in the US by the time of follow-up. Our cohort also represents a group of self-selected individuals who first sought evaluation in our Neuro-COVID-19 clinic and chose to participate in our follow-up study. This is the case for any study performed in an outpatient clinic setting. Although this very specific group is not representative of all non-hospitalized SARS-CoV-2$^+$ individuals, it allowed us to characterize neurologic symptom evolution in an ambulatory setting a median of 14.8 months after symptom onset compared to other studies which only assessed symptoms up to 8 months.[46–48] In addition, we aimed to decrease the selection bias in our initial study by (1) including the first 100 patients presenting to the clinic after it was mentioned on our institution's website, (2) not requiring physician referral or health insurance, and (3) increasing the diversity by including patients seen both in-person and in televisits from 21 US states.

Finally, we focused on patient-reported outcomes for cognition but did not perform cognitive testing, as evaluation with the NIH Toolbox cognitive assessment requires an in-person visit. Since close to half of the first 100 nonhospitalized patients were evaluated in televisits at the

beginning of the pandemic, only a subset of patients had undergone cognitive evaluation. Consequently, in the current study, 34 patients reside in Illinois while the remaining 18 came from 16 other US states. This large spread of patient location further informed our decision to administer follow-up surveys via phone and email and precluded in-person cognitive testing using the NIH Toolbox. Finally, pandemic-related restrictions of in-person interaction with research patients at our institution, further impeded cognitive testing of local participants during the period of follow-up observation.

Moreover, one study has shown high frequency of impairment of cognitive domains such as memory encoding and processing speed in nonhospitalized COVID-19 patients, with a mean of 7.6 months after symptom onset.[47] Given the timing of our initial study and follow-up period, these results only reflect results from initially identified strains of SARS-CoV-2. However, such data will be valuable in evaluating and comparing effects of subsequent strains, including the very contagious Omicron variant.

Our data highlights the need for future research to follow symptom evolution as the pandemic continues and new, more transmissible variants emerge. Our study also emphasizes the significant and persistent symptom burden on "long haulers" far beyond the acute phase of COVID-19, often in patients with mild initial presentation. Long-COVID syndrome is causing a detrimental impact on quality of life and overall productivity which may only continue worsening as the pandemic evolves.

The SARS-CoV-2$^-$ population is a unique cohort that faces difficulty obtaining evaluation and treatment for symptoms suggestive of COVID-19 infection and long COVID. Yet these patients comprised the majority of the non-hospitalized long haulers at the beginning of the pandemic[49] and it has been advocated that a positive test for COVID-19 should not be a prerequisite for diagnosis.[33] In an international patient-led online survey of long COVID symptoms of 3762 participants from 56 countries, only 27.2% were laboratory-confirmed while 72.8% were laboratory-negative or untested for COVID-19.[49] By analogy, since there were ~13 million COVID-19 survivors in the US in November 2020 when we completed enrollment of our initial study and knowing that about a third of them developed long COVID, it is possible that an additional ~10 million people in the US had developed long COVID and tested negative by PCR or antibody for SARS-CoV-2 or could not be tested. This sizeable population constituted predominantly of females in their forties who do not carry a firm diagnosis of COVID-19 has unfortunately experienced much rejection and stigma and are underrepresented in the medical literature.[50,51] Of note, of 64 post-COVID clinics in the US[52] contacted on the phone, only 19 (30%) acknowledged they would accept to see SARS-CoV-2$^-$ "long haulers." Sadly, suppressing publications including those patients only perpetuates their dismissal. Epidemiologic studies should investigate the vast impacts of COVID-19 on non-hospitalized populations and their potential duration. Further research is urgently needed to define the pathogenic mechanism of Neuro-PASC in addition to longitudinal studies to determine best management and treatment modalities for existing cohorts of "long haulers."

Author Contributions

I.J.K., E.L.G, Z.S.O., P.H.L., A.B., and E.M.L conceived and designed the study. Z.S.O. and P.H.L. organized and monitored data acquisition. S.T.A., A.K.K., and T.R.P. acquired data. A.K.K. and Z.S.O performed statistical analysis and generated figures and tables. S.T.A., A.K.K., T.R.P., J.R.C., G.S.P., Z.S.O., P.H.L., M.J., E.L.G., A.B., E.M.L., and I.J.K. contributed to the interpretation of the results. S.T.A., A.K.K., and T.R.P. prepared the manuscript. All authors provided critical feedback and helped shape the research, analysis, and manuscript.

Conflict of Interest

The authors report no conflict of interest pertaining to this publication.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1 Associations between neuro-psychiatric quality of life PROMIS measures. PROMIS quality of life measure of cognitive function was significantly correlated with PROMIS measures of (A) fatigue, (B) anxiety, (C) depression, (D) sleep disturbance at the second visit. (E) Associations between all neuro-psychiatric PROMIS measures are shown in a matrix, where negative correlations are shown in shades of red and positive correlations in shades of blue.

Table S1 Neurologic and other symptoms endorsed by patients, compared between initial clinic visit and follow-up, by SARS-CoV-2 result.

